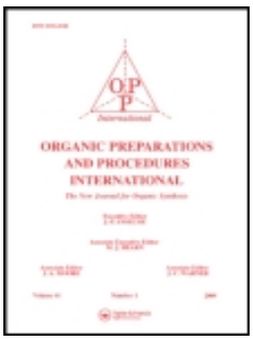

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An Improved Procedure for the Preparation of Apraclonidine Hydrochloride

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Glaucoma is an umbrella term for eye conditions which damage the optic nerve, and which can lead to a loss of vision. The main cause of damage to the optic nerve is intraocular pressure (IOP), excessive fluid pressure within the eye, which can be due to various reasons including blockage of drainage ducts, and narrowing or closure of the angle between the iris and cornea. Standard treatments for glaucoma include eye drops, oral medication and conventional surgery that creates a new opening for fluid to leave the eye.

Apraclonidine hydrochloride (2,6-dichloro-N^1-(4,5-dihydro-1*H*-imidazol-2-yl)-1,4-benzenediamine monohydrochloride, **6**), a clonidine derivative, is a potent and relatively selective α-adrenergic receptor agonist.[1] It does not have significant membrane stabilizing (local anesthetic) activity.[2–5] It was first invented by the Alcon company and launched on the market as an eye drops in America in 1993 under the tradename *Iopidine*®. The name *apraclonidine hydrochloride* was recorded in the United States Pharmacopoeia (USP 35). Most of the published preparations of the title compound focused on 2,6-dichloro-4-nitroaniline (**1**) as the starting material. Thus, Counsell and his group,[6] synthesized apraclonidine (**5**) in four steps from compound (**1**) through formylation with formic acid and acetic anhydride, chlorination with SO_2Cl_2/$SOCl_2$, cyclization with ethylenediamine and reduction of the nitro group with iron powder in 22% overall yield. Subsequently, Pierce *et al*. prepared apraclonidine hydrochloride by treatment of 2,6-dichloro-4-nitroaniline with thiophosgene or carbon disulfide to provide the corresponding isothiocyanate which was condensed with ethylenediamine, followed by cyclization to provide *N*-(2,6-dichloro-4-nitrophenyl)-4,5-dihydro-1*H*-imidazol-2-amine (**4**) in 52% yield. Reduction with Raney nickel in methanol at 50psi pressure gave apraclonidine (**5**). Then hydrogen chloride gas was bubbled into the solution of apraclonidine in methanol until the pH of the reaction mixture is about 1. The solvent was removed and the residue was triturated with 2-propanol and to give apraclonidine dihydrochloride. Finally, apraclonidine hydrochloride (**6**) was obtained by treatment of apraclonidine dihydrochloride with apraclonidine in 87% yield (for this step).[7] Most of these methods require high reaction temperatures, several steps, the use of hazardous reagents (such as thiophosgene) or generate iron sludge pollution. Thus an efficient, environmentally friendly and practical method for the preparation of apraclonidine

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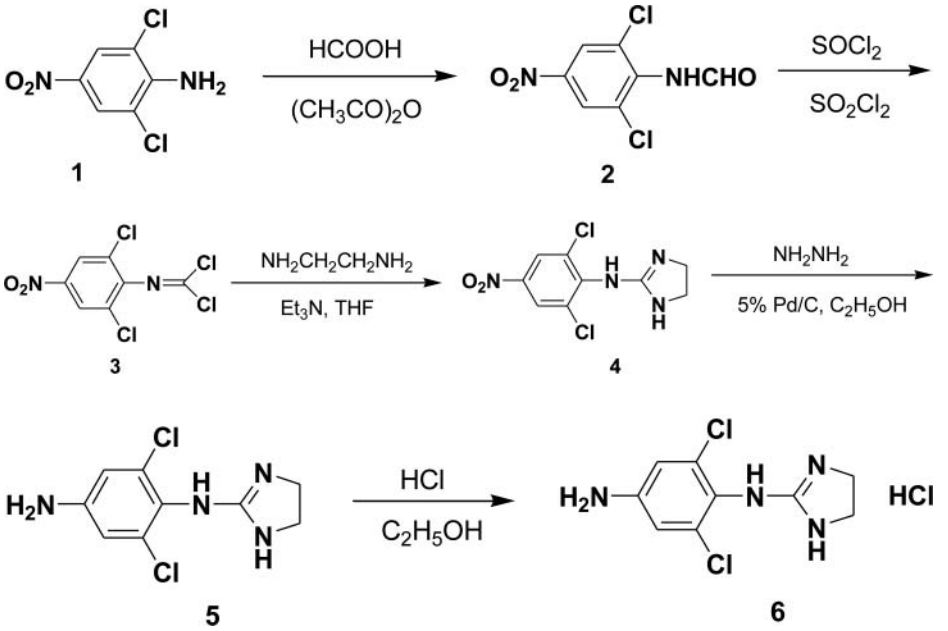
hydrochloride seemed desirable. We now describe an improved procedure based on Counsell's route.[6]

The modifications were focused on the ratio of acetic anhydride and formic acid and simplification of the process, especially for the reduction of the nitro group to amino group by using 85% hydrazine hydrate and 5% Pd/C (*Scheme 1*). Several parameters were explored in an attempt to improve the yield of desired product. The ration of acetic anhydride, formic acid and compound **1** used in the formylation steps is around 1:6:0.9 and avoid *N*-diformylation by-product formation. Product **2** was purified by recrystallization from 95% ethanol instead of column chromatography. The chlorination and cyclization steps proceeded smoothly in THF with 62% yield. Palladized charcoal as a catalyst for the reduction of nitro compounds **4** with hydrazine hydrate was developed.[8–11] The catalyst (5% Pd/C) may be re-used four times, further use led to decreased yields. Finally, apraclonidine hydrochloride **6** was obtained by treatment of apraclonidine with conc. hydrochloric acid (37%) in 95% ethanol. The overall yield of **6** from **1** was 27%. The structures were confirmed by ^{1}H NMR, ^{13}C NMR and MS analysis. This method has many advantages, such as simple operation, low cost, high yields and high purity of the products.



Scheme 1

Experimental Section

Melting points were determined with RY-1 apparatus and are uncorrected. IR spectra were acquired as KBr pellets on a Shimadzu model 470 spectrophotometer. ^{1}H NMR spectra were recorded using a Bruker AV 400 MHz spectrometer in DMSO-d_6 or $CDCl_3$ with tetramethylsilane as internal standard. EI mass spectra were obtained on Shimadzu QP-2010 GC-MS system. All chemicals and reagents were purchased from commercial suppliers and used without further purification.

***N*-(2,6-Dichloro-4-nitrophenyl)formamide (2)**

To 132.0 mL (3.5 mol) of formic acid in a 1 L three-neck round bottom flask, was added 55.2 mL (0.58 mol) of acetic anhydride dropwise over 20 min with mechanical stirring so as to keep the internal temperature at 55–60°C. The reaction mixture was then cooled to ambient temperature. 2,6-Dichloro-4-nitroaniline (**1**, 110.0 g, 0.53 mol) was added within 20 min. and the mixture was heated at 55°C for 6 h. After the completion of the reaction as monitored by TLC (GF_{254}, silica gel, *n*-hexane:ethyl acetate 4:1), the mixture was evaporated under reduced pressure (about 80 mmHg) to give a yellow solid. Then, 500 mL water was added and stirring continued for 10 min (mechanical stirring). The solid product was collected, washed with water and recrystallized from 95% EtOH to give *N*-(2,6-dichloro-4-nitrophenyl)formamide **2** as a pale yellow solid (80.6 g, 65%), mp. 158–160°C. (*lit*.[6] 158.5–159.5°C).

^{1}H NMR($CDCl_3$): δ 7.43 (s, 1H, NH), 8.32 (s, 2H, Ar-H), 8.61 (s, 1H, CHO). MS (EI,70eV): m/z 234 $[M]^+$,199,176,124,97.

(2,6-Dichloro-4-nitrophenyl)carbonimidic Dichloride (3). *N*-(2,6-dichloro-4-nitrophenyl) formamide (50.5 g, 0.22 mol) was added to a mixture of $SOCl_2$ (70.0 mL, 0.97 mol) and SO_2Cl_2 (35.0 mL, 0.43 mol) over 15 min. The mixture was heated to 60°C and stirred using magnetic stir bar until *N*-(2,6-dichloro-4-nitrophenyl)formamide was consumed (at least 8 h, monitored by TLC, GF_{254}, silica gel, *n*-hexane:ethyl acetate 4:1). Evaporation under reduced pressure (about 60 mmHg) afforded a red-brown oil that was used directly without further purification in the next step.

***N*-(2,6-Dichloro-4-nitrophenyl)-4,5-dihydro-1H-imidazol-2-amine (4)**. Ethylenediamine (13.2 g, 0.22 mol), triethylamine (44.5 g, 0.44 mol) and tetrahydrofuran (300 mL) were added to a 1L three-neck round bottom flask and the mixture was stirred (mechanical stirring) in an ice bath for 15 min. Then a solution of **3** in tetrahydrofuran (50 mL) was added dropwise into this reaction mixture at 5–10°C over about 0.5 h. The mixture was stirred for 6 h at room temperature until the starting material was consumed (monitored by TLC, GF_{254}, silica gel, *n*-hexane:ethyl acetate 3:1). The solvent was removed by distillation under reduced pressure (about 60 mmHg). Water 400 mL was added and the mixture was stirred for 10 min. The solid formed was collected, dried overnight and purified by recrystallization from 95% EtOH to provide the product **4** as a yellow solid (36.7 g, 62%), mp. 287–289°C (*lit*.[6] 283–285°C). ^{1}H NMR(DMSO-d_6): δ 3.41 (s, 4H, CH_2), 6.74 (s, 2H, Ar-H), 8.16 (s, 2H, 2NH). ^{13}C NMR(DMSO-d_6): δ 42.26, 123.94, 128.77, 139.62, 153.97, 157.63. MS(EI,70eV): m/z 275 $[M]^+$, 255, 213, 161, 107, 81.

2,6-Dichloro-N^1-(4,5-dihydro-1H-imidazol-2-yl)-1,4-benzenediamine (5). To a suspension of compound **4** (27.4 g, 0.1 mol) and 5% Pd/C (0.3 g) in 95% ethanol (200 mL), was added 85% hydrazine hydrate (11.8 g, 0.2 mol) dropwise (40 min.) at room temperature. The mixture was heated at reflux for 8 h and then the hot solution was filtered immediately using suction to remove the Pd/C. Upon cooling the filtrate to room temperature, the precipitated solid was collected and recrystallized from 95% EtOH to afford 19.1 g (78%) of apraclonidine (**5**) as a yellowish white solid, mp. 225–227°C (*lit*.[6] 227–229°C). ^{1}H NMR (DMSO-d_6): δ 3.26 (s, 4H, CH_2), 4.97 (s, 2H, 2NH), 5.91 (brs, 2H, NH_2), 6.55 (s, 2H, Ar-H). ^{13}C NMR (DMSO-d_6): δ 42.33, 114.19, 129.19, 135.38, 143.98, 158.37. MS(EI,70eV): m/z 246, 244$[M]^+$, 209, 186, 174, 139, 124, 99, 73.

2,6-Dichloro-N^1-(4,5-dihydro-1H-imidazol-2-yl)-1,4-benzenediamine Hydrocchloride (6). A mixture of compound **5** (24.4 g, 0.1 mol) and conc. HCl (9.2 mL, 0.11 mol) in 250 mL of 95% ethanol was refluxed for 30 min. Upon cooling to room temperature, the colorless product which precipitated was collected, recrystallized from 95% ethanol and dried to give apraclonidine hydrochloride **6** (23.4 g, 84%) as a colorless solid, mp. 303–305°C (*lit.*[7] 300°C). ^{1}H NMR(DMSO-d_6): δ 3.60–3.67 (d, 4H, CH_2), 6.08 (s, 2H, NH_2), 6.73 (s,2H,Ar-H), 8.31 (s, 1H, NH), 8.44 (s, 1H, NH), 10.20 (s, 1H, HCl). ^{13}C NMR (DMSO-d_6): δ 43.25, 113.26, 116.98, 134.54, 151.19,1 59.55. MS(EI,70eV): m/z 246, 244[M-HCl]$^+$, 209, 186, 174, 139, 124, 99, 73. HRMS(EI,70eV): Calcd for $C_9H_{10}N_4Cl_2$ [M-HCl]$^+$ 244.0283, Found 244.0287.

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